



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 53702

Title: Innate immune recognition and modulation in Hepatitis Delta Virus infection

Reviewer's code: 02528812

Position: Editorial Board

Academic degree: PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Iran

Author's Country/Territory: Germany

Manuscript submission date: 2019-12-29

Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-01-04 09:00

Reviewer performed review: 2020-01-04 10:47

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

SPECIFIC COMMENTS TO AUTHORS

This review study is well written and well organized. In this study, the authors have demonstrated what is known up-to-date about the innate immune recognition and modulation in HDV infection as well as the interplay between HBV and HDV's immune evasion strategy. Although, there are many unknown remains in this regards. Generally, this is an informative and valuable review study.



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 53702

Title: Innate immune recognition and modulation in Hepatitis Delta Virus infection

Reviewer's code: 02528222

Position: Peer Reviewer

Academic degree: PhD

Professional title: Research Assistant Professor

Reviewer's Country/Territory: Russia

Author's Country/Territory: Germany

Manuscript submission date: 2019-12-29

Reviewer chosen by: AI Technique

Reviewer accepted review: 2019-12-29 20:20

Reviewer performed review: 2020-01-07 22:44

Review time: 9 Days and 2 Hours

Scientific quality	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

The review by U. Protzer's group describes current understanding of interplay between hepatitis delta virus (HDV) infection and innate immune response, and with viral RNA sensors in a host cell in particular. The title clearly shows the topic of the review. In the text the authors provide a brief but very informative background of HDV molecular biology and life cycle. Then it states which sensors are used by the virus, presents an overview of an influence of hepatitis B virus on interferon response, and discusses it basing on the data from various systems used in the field. Finally, the authors briefly present current understanding what is an impact of interferons on HDV infection. The text is very clearly and concisely written and is very informative. The review is citing all the key references in the field. So, in my understanding it can be published in the current form. At the same time I have three comments that are suggestions rather than requirements. 1. The authors always refer to type I interferons. It could be worth mentioning that HDV can trigger production of type III interferons as well by the same PRR. Actually, the reference 24 contains this data. 2. While discussing HDVAg overexpression and activation of the NFkB factor, it could be mentioned that protein overexpression can lead to ER Overload Response (EOR) (see R. Kaufman's reviews) that does result in NFkB activation. It could serve as a nice speculation to the assumption that the effect could be due to simple overexpression of HDVAg. 3. I may have missed discussion if HDV does (or does not) induce IFN production in patients. Actually, I am not aware if such data exist. But in any case existence/absence of such data could be mentioned.



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 53702

Title: Innate immune recognition and modulation in Hepatitis Delta Virus infection

Reviewer's code: 00506601

Position: Peer Reviewer

Academic degree: PhD

Professional title: Doctor

Reviewer's Country/Territory: United States

Author's Country/Territory: Germany

Manuscript submission date: 2019-12-29

Reviewer chosen by: Jie Wang

Reviewer accepted review: 2020-01-07 13:29

Reviewer performed review: 2020-01-08 19:46

Review time: 1 Day and 6 Hours

Scientific quality	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

This is a wonderful review of Hepatitis Delta Infection (77 references) and is thorough and comprehensive. I really enjoyed reading the paper and it was very informative. I can't wait until it is published so I can share it with my colleagues. I have only one suggestion, which is to break up the four-line sentence at the bottom of the middle paragraph under the heading "Impact of HBV Coinfection" (page 6). I would write that sentence as follows: An inhibition of interferon responses by HBV, however, has also been described in mice with humanized livers. One would expect these livers to be close to the human physiological situation although HBV replication levels maybe higher due to the lack of adaptive immunity and a cross-talk between human hepatocytes and murine non-hepatocytes. This is just a suggestion but the sentence, as it stands now, is confusing and is definitely a run-on sentence. Otherwise the English is perfect, and I loved the paper



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 53702

Title: Innate immune recognition and modulation in Hepatitis Delta Virus infection

Reviewer's code: 00003629

Position: Editorial Board

Academic degree: MD

Professional title: Emeritus Professor

Reviewer's Country/Territory: Greece

Author's Country/Territory: Germany

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Reviewer chosen by: Jie Wang

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Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

The article by Jung S et al, entitled "Innate Immune Recognition and Modulation in Hepatitis Delta Virus Infection", addresses the complicated and difficult subject of the immune response, or more precisely the lack of an immune response in HBV and HDV co-infection. From a virological and immunological point of view the article is very well written and easy to understand. Special mention should be also made of the two figures listed in the article and their concise note. The authors, and in particular the corresponding author, are well known for their research activity in virology and especially hepatitis B virus. However, clinically, the article needs improvement. One would expect more reference on issues concerning the natural progression of the acute and chronic HDV infection and its medical treatment. More specifically, I would like the authors to refer and answer questions such as: a. What is the immunological background of acute HBV-HDV co-infection? In that situation there is a strong, often excessively so, immune response usually leading to clearance of the infection and sometimes to death. What is the role of HDV as opposed to HBV? b. What is the immunological background of the frequent transition to chronicity of the acute HDV superinfection? c. What is the underlying immunological cause of the rapid evolution to cirrhosis and hepatic failure of patients with hepatitis delta? Since HDV stimulates the immune system very little, why is the evolvement of chronic delta infection rapid, even faster than the (simple) chronic HBV infection? d. Authors could further emphasize the therapeutic antiviral activity of interferon at an immunological level, and provide possible explanations for why this beneficial effect is not observed in most patients. I believe that with improvements, as suggested above, the article will attract, among else, wider clinically oriented readership.



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

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Title: Innate immune recognition and modulation in Hepatitis Delta Virus infection

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Reviewer's Country/Territory: Italy

Author's Country/Territory: Germany

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Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

The manuscript describes an interesting issue, and it's concisely and clearly described. It makes a pleasant and useful reading for those in the field and for readers of the Journal.